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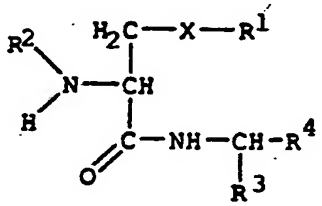
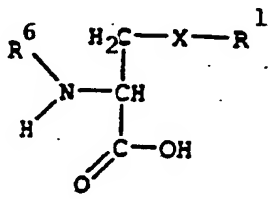


(I)



(II)

(57) Abstract

The present invention relates to amides of general formula (I), a process for the preparation thereof and pharmaceutical compositions containing them. In formula (I), X is oxygen or sulphur; R^1 is alkyl; R^2 is hydrogen, alkylcarbonyl, alkoxycarbonyl or alkylsulfonyl or the corresponding arylalkyl groups; R^3 is hydrogen, carboxyl, alkoxycarbonyl or aryloxycarbonyl; and R^4 hydrogen, alkyl, arylalkyl, heteroarylalkyl, hydroxyalkyl, thioalkyl, alkylthioalkyl, aminoalkyl, carboxyalkyl, carbamoyl, guanidinoalkyl or sulfoalkyl. Said compounds inhibit phospholipase A_2, therefore they can be used as antiinflammatory, antiallergic, antithrombotic, antiasthmatic agents and in the prevention of anaphylactic shock. Said amides can be obtained by reacting a compound (II), wherein R^6 is the same as R^2 or a suitable protecting group, with a suitable amine $H_2NCHR^3R^4$, in the presence of a proton-binding base and a carboxy-activating agent.

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AMIDES HAVING INHIBITING ACTIVITY ON PHOSPHOLIPASE A_2, A PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

FIELD OF THE INVENTION

The present invention relates to novel amides, a process for the preparation thereof, the pharmaceutically acceptable salts thereof and pharmaceutical compositions containing them.

Said amides have inhibiting action on phospholipase A_2.

TECHNOLOGICAL BACKGROUND

It is well established that the major part of eicosanoids, prostaglandins and related compounds derive from a C_{20} fatty acid, having 4 insaturations, which is named arachidonic acid (AA), which is mainly obtained esterifying the hydroxy group at the 2-position of glycerophospholipids contained in cell membranes. AA is released from the phospholipid containing it by the action of a lipase, i.e. phospholipase A_2 (PLA_2) ("CRC Handbook of Eicosanoids and Related Lipids", vol. (II), Ed. A. L. Willis, CRS Press, Inc. Florida (1989)). After the release, AA is metabolized in mammals through different pathways or enzyme systems. Through cyclooxygenase, AA gives rise to prostaglandins and thromboxanes, the most significant being PGE_2 and TxA_2, which participate directly in inflammation (Higgs et al. Annals of Clinical Research, 16, 287-299 (1984)). Through lipooxygenase, AA produces leukotrienes, the most important being LTB_4, LTC_4 and LTD_4, which also participate in inflammatory reactions, showing chemotactic activities, stimulate segregation of

lysosomal enzymes and act as important factors in the immediate hypersensitivity reactions (Bailey and Casey, Ann. Rep. Med. Chem., 17, 203-217 (1982)).

By the action of PLA_2, besides the release of fatty acids, the corresponding lysophospholipids are obtained, which either can then be re-esterified or be converted into PAF (platelet activating factor) by acetylation at 2-position, if they have phosphocholine at the 3-position, an ether bond at the 1-position and are in a cell system having acetyl-transferase activity. PAF is also a pro-inflammatory agent, that has been ascribed to play an important role in various pathological processes, such as asthma, anaphylaxis, inflammation and ischemia (Braquet et al., Pharmacol. Rev., 39 (2), 97 (1987)).

PLA_2, besides being related to the inflammatory processes, can also be involved, either directly or indirectly, in degenerative thrombotic and cancerous pathologies.

From what stated above, it is evident that PLA_2 is of great importance in controlling the production of the mediators involved in the pathologies indicated above. As a consequence, compounds inhibiting PLA_2 provide a new rational approach for the prevention, elimination or improvement of different allergic, anaphylactic, asthmatic, inflammatory and thrombotic conditions.

Various compounds have been described to be <u>in vitro</u> inhibitors of PLA_2 (Wilkerson, Drugs of the Future, 15, 141 (1990)), however nowadays there are no specific PLA_2 inhibitors for the clinical use.

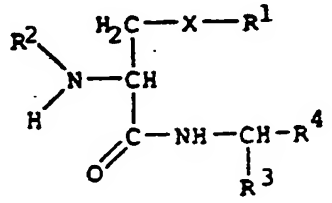
The compounds of general formula (I) are not

structurally related to any PLA_2 inhibitor described in literature. Some compounds that could be considered structurally related to the compounds of the present invention are not included in formula (I) and show very different activities, for example some of them are receptor inhibitors of LTC_4, (Sala et al., Eicosanoids, 3, 105 (1990)), or of glutathione S-transferase (Adang et al., J. Biol. Chem., 266, 830 (1991)), or they enhance the immune activity (JP 55085553); or they are S-butylglutathione-like metabolites (James et al., Biochem. J. 109, 727 (1968)).

Up to now, corticosteroids are the only medicaments considered likely to exert an inhibitory mechanism on PLA_2, even though in an indirect way. However, said compounds have a series of adverse systemic side-effects which restrict the use thereof, particularly in chronic pathologies. PLA_2 selective inhibitors, such as the compounds of the present invention, advantageously have the same effectiveness as corticosteroids, without the side-effects thereof.

DISCLOSURE

The compounds of the present invention have the following general formula (I)



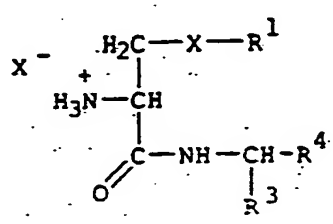
I

wherein:

- X is an oxygen or sulphur atom;

- R^1 is a C_4-C_{20} straight or branched alkyl group;
- R^2 is hydrogen or a R^5-CO-, R^5-O-CO- or R^5-SO_2- group, in which R^5 is a C_1-C_{20} straight or branched alkyl group, phenyl or an arylalkyl group of less than 20 carbon atoms totally;
- R^3 is hydrogen, a carboxy group, an alkoxycarbonyl, aryloxycarbonyl or arylalkoxycarbonyl group of less than 10 carbon atoms in the last three cases;
- R^4 is hydrogen, a C_1-C_6 straight or branched alkyl group, an arylalkyl group of less than 10 carbon atoms, an heteroarylalkyl group of less than 10 carbon atoms, an hydroxyalkyl group of less than 4 carbon atoms, a thioalkyl or alkylthioalkyl group of less than 4 carbon atoms, an aminoalkyl group of less than 6 carbon atoms, the amino group being in the free or derivatized form, as an alkyl amide of less than 4 carbon atoms, a C_2-C_5 carboxyalkyl group, the carboxy group being in the free or derivatized form as an alkyl or aralkyl ester of less than 8 carbon atoms, a carbamoylalkyl group of less than 4 carbon atoms, a guanidinoalkyl group of less than 5 carbon atoms, or a sulfoalkyl group of less than 4 carbon atoms; with the proviso that R^4 cannot be hydrogen when R^3 is hydrogen or when R^1 is C_4 alkyl and R^2 is hydrogen or acetyl.

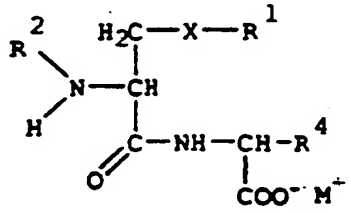
When R^2 is hydrogen, the compounds of formula (I) can be obtained in form of salts, as represented by formula (Ia)



Ia

wherein X^- is a pharmaceutically acceptable anion of an inorganic acid (e.g. hydrochloric or sulfuric) or organic carboxylic acid (e.g. acetic, trifluoroacetic, lactic or tartaric), or organic sulfonic acid (e.g. methanesulfonic, ethanesulfonic or toluenesulfonic).

When R^3 is a carboxy group, the compounds of formula (I) can also be obtained in form of salts, as represented by formula (Ib)



Ib

wherein M^+ is an alkali metal cation (e.g. Na^+, K^+), or the equivalent of an alkaline-earth metal cation (e.g. $1/2\ Ca^{2+}$, $1/2\ Mg^{2+}$).

When the compounds of formula (I) have more than one basic nitrogen, the double acid addition salts can also be obtained (e.g. dihydrochlorides or dihydrobromides). Similarly, when the compounds of formula (I) have more than one carboxylic or sulfonic acid group, the double base addition salts can also be obtained (e.g. sodium, potassium, calcium or magnesium salts).

The compounds of general formula (I) have one or more asymmetric carbons in their structure. The present invention includes all the possible stereoisomers as well as the mixtures thereof.

In the compounds of general formula (I), R^1 can be for example butyl, hexyl, decyl, tetradecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl or icosyl; when R^2 is

a R^5-CO-, R^5-O-CO- or R^5-SO_2-, in which R^5 is an alkyl or arylalkyl group, this can be methyl, ethyl, propyl, butyl, decyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, benzyl or 11-phenylundecyl; when R^3 is an alkoxycarbonyl, aryloxycarbonyl or arylalkoxycarbonyl group, they can be methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl; when R^4 is an alkyl group, this can be methyl, isopropyl, butyl, isobutyl or sec-butyl; when R^4 is an arylalkyl group, this can be benzyl or p-hydroxybenzyl; when R^4 is an heteroarylalkyl group, this can be 4-imidazolylmethyl or 3-indolylmethyl; when R^4 is an hydroxyalkyl group, this can be hydroxymethyl, 1-hydroxyethyl or 2-hydroxyethyl; when R^4 is a thioalkyl or alkylthioalkyl group, this can be mercaptomethyl or 2-methylthioethyl; when R^4 is an aminoalkyl group, this can be 4-aminobutyl, 3-aminopropyl or 4-acetylaminobutyl; when R^4 is a carboxyalkyl group, this can be carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, methoxycarbonylmethyl or 2-methoxycarbonylethyl; when R^4 is a carbamoylalkyl group, this can be carbamoylmethyl or 2-carbamoylethyl; when R^4 is a guanidinoalkyl group, this can be 2-guanidinoethyl or 3-guanidinopropyl; when R^4 is a sulfoalkyl group, this can be sulfomethyl, 2-sulfoethyl or 3-sulfopropyl.

Preferred compounds of the present invention are those in which:

- X and R^1 are the groups defined above;
- R^2 is hydrogen, a C_1-C_{21} alkoxycarbonyl group atoms, preferably groups acetyl, hexanoyl, dodecanoyl or hexadecanoyl;

- R^3 is hydrogen, a carboxy group or an alkoxycarbonyl group of less than 10 carbon atoms, preferably methoxycarbonyl or ethoxycarbonyl;
- R^4 is hydrogen, a C_1-C_6 straight or branched alkyl group, preferably methyl or isobutyl, an hydroxyalkyl group of less than 4 carbon atoms, preferably hydroxymethyl or 2-hydroxyethyl, an aminoalkyl or alkylcarbonylaminoalkyl group of less than 7 carbon atoms totally, preferably 4-aminobutyl or 4-acetylaminobutyl, a C_2-C_5 carboxyalkyl group, preferably carboxymethyl or 2-carboxyethyl, or a sulfoalkyl of less than 4 carbon atoms, preferably sulfomethyl.

Particularly preferred compounds of the present invention are the following:

N-Hexanoyl-O-octadecyl-D-serinyl-L-valine.
N-Hexadecanoyl-O-decyl-D-serinylglycine.
N-Acetyl-O-octadecyl-D-serinyl-L-glutamic acid.
N-Acetyl-O-octadecyl-D,L-serinyl-L-glutamic acid.
N-Acetyl-O-octadecyl-D-serinyl-D-glutamic acid.
N-Acetyl-O-octadecyl-D,L-serinyl-L-leucine.
N-Acetyl-O-octadecyl-D,L-serinyl-D,L-leucine.
N-Acetyl-O-octadecyl-D-serinyl-L-leucine.
N-Hexadecanoyl-S-decyl-D-cysteinyl-L-lysine.
N-Acetyl-S-octadecyl-D-cysteinyl-L-lysine.
S-Octadecyl-D-cysteinylglycine (hydrobromide).
S-Octadecyl-D-cysteinyl-L-lysine (hydrobromide).
S-Octadecyl-L-cysteinyl-L-lysine (hydrobromide).
S-Octadecyl-D-cysteinyl-D-lysine (hydrobromide).
S-Octadecyl-L-cysteinyl-D-lysine (hydrobromide).
S-butyl-D-cysteinyl-L-glutamic acid (hydrobromide).
S-Butyl-D-cysteinyl-L-leucine (hydrobromide).

S-Butyl-D-cysteinyl-L-lysine (hydrobromide).

N-Acetyl-S-octadecyl-D-cysteinyl-L-leucine.

N-Acetyl-S-octadecyl-D,L-cysteinyl-D,L-leucine.

N-Acetyl-S-octadecyl-D-cysteinylglycine.

Methyl N-acetyl-S-octadecyl-D-cysteinyl-L-glutamate.

N-Acetyl-S-octadecyl-D-cysteinyl-L-glutamic acid.

N-Acetyl-S-octadecyl-D-cysteinyl-ε-N-acetyl-L-lysine.

N-Acetyl-S-octadecyl-L-cysteinyl-ε-N-acetyl-L-lysine.

N-Acetyl-S-octadecyl-D-cysteinyl-ε-N-acetyl-D-lysine.

N-Acetyl-S-octadecyl-L-cysteinyl-ε-N-acetyl-D-lysine.

N-Acetyl-S-octadecyl-D-cysteinyl-L-serine.

N-Acetyl-S-octadecyl-D-cysteinyl-L-homoserine.

N-Dodecanoyl-S-butyl-D-cysteinyl-L-glutamic acid.

N-Dodecanoyl-S-butyl-D-cysteinyl-L-leucine.

N-Acetyl-S-butyl-D-cysteinyl-ε-N-acetyl-L-lysine.

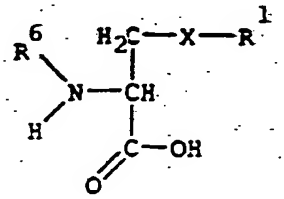
N-Acetyl-S-octadecyl-D,L-cysteinyltaurine (sodium salt).

N-Acetyl-S-decyl-D,L-cysteinyltaurine (sodium salt).

N-Acetyl-S-octadecyl-D-cysteinyltaurine (sodium salt).

N-Acetyl-S-octadecyl-D-serinyltaurine (sodium salt).

According to the present invention, the compounds of general formula (I) can be prepared by reacting a compound of formula (II), of suitable stereochemistry at the carbon at the 2-position

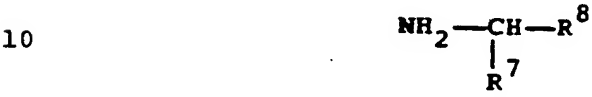


II

wherein X and R^1 are the groups defined above and R^6

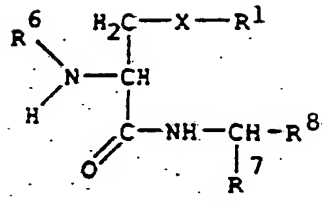
can be equivalent to the group R^2 above or, if R^2 in formula (I) is hydrogen, then R^6 is a suitable amino-protecting group, for example benzyloxycarbonyl or tert-butyloxycarbonyl, with:

a) When in (I) R^3 is one of the groups defined above, except for hydrogen, and R^4 is one of the groups defined above, except for a sulfoalkyl group, a reactive of formula (III), of suitable stereochemistry,



III

wherein R^7 can be equivalent to R^3 in formula (I), except for hydrogen, and, when in (I) R^3 is a carboxy group, then R^7 is a suitably protected carboxy group, for example in form of the benzyl or tert-butyl ester, and R^8 can be the same as R^4, except when in formula (I) R^4 contains a functional group in the free form, in which case in R^8 such a group is suitably protected, for example when R^4 in formula (I) contains an amino group, R^8 in formula (III) can contain a benzyloxycarbonylamino or tert-butyloxycarbonylamino group; when R^4 in (I) contains a carboxy group, this is for example in form of the benzyl or tert-butyl ester in (III); the reaction between (II) and (III) is carried out in the presence of a proton-binding base, such as triethylamine or pyridine and a carboxy-activating agent, such as dicyclohexylcarbodiimide or pivaloyl chloride, in suitable aprotic solvents such as chloroform, methylene chloride or N,N-dimethylformamide, at a temperature from 0° to 40°C for a time from 3 to 24 hours, to obtain an intermediate of formula (IV)



IV

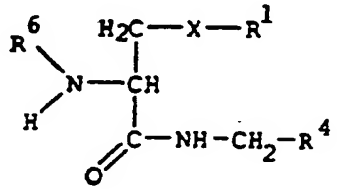
wherein X, R^1, R^6, R^7 and R^8 are the groups described above. This compound of formula (IV) is converted into (I) by removing any protecting groups present in R^6, R^7 and R^8, according to conventional methods; when R^6 and R^7 are benzyloxycarbonyl groups and a benzyloxycarbonylamino or a benzyloxycarbonyl group can be present in R^8, the benzyl groups can be removed by catalytic hydrogenation with Pd-C or with $Pd(OH)_2$, in solvents such as methanol, water or acetic acid, under hydrogen pressures from atmospheric pressure to 50 psi, at a temperature from 20° to 50°C for a time from 3 to 20 hours; or in an acid medium, for example with hydrobromic or trifluoroacetic acid, in a suitable solvent such as acetic acid or chloroform, at a temperature from 0° to 40°C for a time from 15 minutes to 6 hours; when R^6 and R^7 are tert-butyloxycarbonyl groups and a tert-butyloxycarbonylamino or tert-butyloxycarbonyl group can be present in R^8, the tert-butyl groups can be removed under the same acid conditions as mentioned above. If R^6 in formula (IV) is an amino-protecting group, such as benzyloxycarbonyl or tert-butyloxycarbonyl, this is deprotected to obtain compounds of formula (I) wherein R^2 is hydrogen, which can in their turn be converted into the compounds (I) with R^2 different from hydrogen by an acylation or sulfonylation reaction with suitable acid

halides or anhydrides (R^5COX, R^5OCOX or R^5SO_2X).

b) When in (I) R^3 is hydrogen and R^4 is a sulfoalkyl group of less than 4 carbon atoms, a compound of formula (II) is reacted with a carboxy-activating agent such as N-hydroxy-5-norbornen-2,3-dicarboxymide acid or N-hydroxysuccinimide in the presence of a dehydrating agent such as dicyclohexylcarbodiimide, in a suitable solvent such as dioxane, tetrahydrofuran or N,N-dimethylformamide, at a temperature from 0° to 40°C for a time from 5 to 24 hours. Subsequently, it is reacted with a reactive (V)

$$NH_2-CH_2-R^4 \qquad V$$

wherein R^4 is a sulfoalkyl group of less than 4 carbon atoms, in the presence of a base such as sodium bicarbonate or aqueous sodium hydroxide, in a suitable organic solvent such as dioxane or tetrahydrofuran at a temperature from 0°C to the solvent's reflux, for a time from 5 to 24 hours, to obtain a compound of formula (VI)



VI

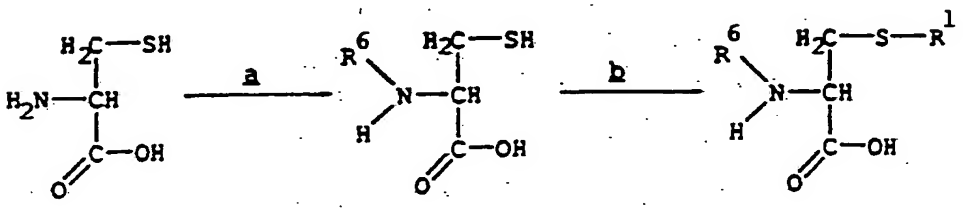
wherein X, R^1, R^4 and R^6 are group described above. When R^6 is the same as R^2, this compound (VI) coincides with compound (I) wherein R^3 is hydrogen and with the proviso that R^2 is hydrogen. When R^6 is an amino-protecting group, this compound can be transformed into compound (I) wherein R^2 is hydrogen, by means of con-

ventional deprotection methods, or optionally it can be converted into the remaining compounds (I), as indicated above.

Finally, if a salt of (I) is desired, a treatment with a suitable acid, base or ion exchanger is carried out, according to conventional methods.

A starting compound (II) wherein X is sulphur can be prepared, for example, following the synthetic sequence shown in Scheme 1.

Scheme 1



VII VIII II(X=S)

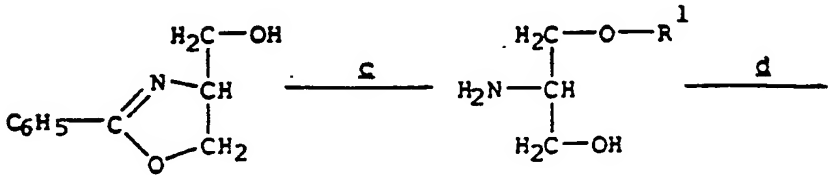
A compound of formula (VIII) wherein R^6 is one of the groups defined above can be obtained (step a) starting from cysteine ((VII)) of suitable stereochemistry, this product being commercially available in both the chiral D or L forms and the racemic one, by reaction with a suitable acyl or sulfonyl halide R^6Y, wherein R^6 is the group described above and Y can be iodide, chloride or bromide, in the presence of a base such as triethylamine, sodium acetate or sodium bicarbonate, in a suitable solvent such as water or N,N-dimethylformamide, at a temperature from 0°C to the solvent's reflux, for a time from 1 to 12 hours.

A compound of formula (II) can be obtained (step b) by reacting the compound (VIII) with a compound ZR^1,

wherein R^1 is the group described above and Z is a suitable leaving group, such as for example bromide, iodide, mesylate or tosylate in the presence of a base such as potassium hydroxide or sodium carbonate, in a suitable organic solvent such as ethanol or N,N-dimethylformamide, at a temperature from 0° to 50°C, for a time from 5 to 24 hours.

A starting compound (II) wherein X is oxygen can be prepared, for example, following the synthetic sequence shown in Scheme 2.

Scheme 2



IX X

XI II(X=O)

A compound of formula (X) can be prepared, for example, starting from compound (IX), the preparation of which is well described in literature (Hajdu et al. J. Org. Chem. 48, 1197 (1983)), by means of a process already described in Spanish Patent application N° 9101610.

A compound of formula (XI), wherein R^1 and R^6 are the groups defined above, can be obtained (step d), by

means of reaction with a suitable acyl or sulfonyl halide as described above.

A compound of formula (II) wherein X is oxygen can be prepared, for example, by subjecting a compound (XI) to the action of an oxidizing agent such as the system formed by $RuCl_3.3H_2O/NaIO_4$, in mixtures of suitable solvents such as carbon tetrachloride:acetonitrile:water (3:3:2) or carbon tetrachloride:ethyl acetate:water (3:3:2), at a temperature from -20° to 30°C, for a time from 15 min to 18 hours.

The compounds of the present invention show a marked activity as inhibitors of PLA_2 activity, and accordingly they have antiinflammatory and antiallergic properties which make them useful for the treatment of diseases in which this enzyme is involved. For this purpose, said compounds can be used in human therapy for the prevention and treatment of allergic rhinitis, bronchial asthma, hypersensitivity reactions such as allergic conjunctivitis, various inflammatory conditions such as those present in rheumatoid arthritis, osteoarthritis, tendinitis, bursitis, psoriasis and other related inflammations.

For the therapeutical uses, the compounds of the present invention are formulated in the appropriate pharmaceutical form, according to conventional techniques and excipients, such as those described in Remington's Pharmaceutical Science Handbook, Mack Pub. Co., N.Y., USA. Examples of said forms include capsules, tablets, syrups and the like, containing from 1 to 1000 mg per unitary dose.

The following examples illustrate the preparation

and the pharmacological activity of the compounds of the present invention.

EXAMPLE 1

N-Benzyloxycarbonyl-D-cysteine ((VIII), R^6=$COOCH_2C_6H_5$).

A solution of D-cysteine (1.50 g, 8.54 mmol) in water (5 ml) is added, at 0°C, with 1M $NaHCO_3$ (25.62 ml) and 1.32 ml (9.41 mmol) of benzyl chloroformate. The mixture is stirred at 0°C for 4 h. After that, it is left at room temperature and the benzyl chloroformate excess is removed by means of extraction with ethyl ether. The resulting aqueous phase is acidified with concentrated hydrochloric acid to pH=3, extracted with ethyl acetate, dried and solvent is removed, to obtain the title compound in an 87% yield.

T.L.C.: eluent chloroform:methanol:acetic acid, 65:25:3, R_f=58

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 3.01 (m, 2H); 4.68 (m, 1H); 5.08 (s, 2H); 7.35 (broad s, 5H).

EXAMPLE 2

N-Benzyloxycarbonyl-L-cysteine ((VIII), R^6=$COOCH_2C_6H_5$).

Following the process described in example 1, starting from L-cysteine, the title compound was prepared in a 93 % yield.

T.L.C.: eluent chloroform:methanol:acetic acid, 65:25:3, R_f=0.58

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 3.01 (m, 2H); 4.68 (m, 1H); 5.08 (s, 2H); 7.35 (broad s, 5H).

EXAMPLE 3

N-Benzyloxycarbonyl-S-octadecyl-D-cysteine ((II), X=S, R^1=$(CH_2)_{17}CH_3$, R^6=$COOCH_2C_6H_5$).

A solution of N-benzyloxycarbonyl-D-cysteine (1.67

g, 6.51 mmol) in ethanol (13.4 ml) is added with 0.36 g (6.51 mmol) of KOH dissolved in ethanol (13.4 ml) under inert atmosphere. The mixture is cooled to 5°C and 1-bromooctadecane (2.17 g, 6.51 mmol) and 0.36 g more of KOH in ethanol are added. The mixture is stirred at room temperature for 24 h. Subsequently, water (100 ml) is added to the mixture, which is acidified with concentrated hydrochloric acid to pH=3-4, extracted with ethyl acetate, dried and solvent is removed, to obtain a crude product which is purified by flash chromatography on silica gel column. Eluting with chloroform:methanol, 20:1, 2.44 g of the title compound are obtained as a white solid melting at 79-81°C (74% yield).

$[\alpha]_D^{20}$ = -7.5° (c=1.164, $CHCl_3$).

T.L.C.: eluent chloroform:methanol:water,65:25:4, R_f= 0.76

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.85 (t, 3H); 1.25 (m, 30H); 1.51 (m, 2H); 2.49 (t, 2H); 2.98 (d, 2H); 4.58 (m, 1H); 5.10 (s, 2H); 7.30 (m, 5H).

EXAMPLE 4

N-Benzyloxycarbonyl-S-octadecyl-L-cysteine ((II), X=S, $R^1=(CH_2)_{17}CH_3$, $R^6=COOCH_2C_6H_5$).

Following the process described in example 3, starting from N-benzyloxycarbonyl-L-cysteine and 1-bromooctadecane the title compound was prepared, 78-81°C (87% yield).

$[\alpha]$ = +7.6° (c=1.163, $CHCl_3$)

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f= 0.76

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.85 (t, 3H); 1.25

(m, 30H); 1.51 (m, 2H); 2.49 (t, 2H); 2.98 (d, 2H); 4.58 (m, 1H); 5.10 (s, 2H); 7.30 (m, 5H).

EXAMPLE 5

N-Benzyloxycarbonyl-S-butyl-D-cysteine ((II), X=S, $R^1=(CH_2)_3CH_3$, $R^6=COOCH_2C_6H_5$).

Following the process described in example 3, starting from N-benzyloxycarbonyl-D-cysteine and 1-bromobutane, the title compound was prepared in a 73 % yield.

T.L.C.: eluent chloroform:methanol:water, 65:25:4, $R_f=0.44$

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.85 (t, 3H); 1.32 (m, 2H); 1.50 (m, 2H); 2.49 (t, 2H); 2.98 (d, 2H); 4.58 (m, 1H); 5.10 (s, 2H); 7.30 (m, 5H).

EXAMPLE 6

Benzyl N-benzyloxycarbonyl-S-octadecyl-D-cysteinyl-γ-benzyl-L-glutamate ((IV), X=S, $R^1=(CH_2)_{17}CH_3$, R^6 and $R^7=COOCH_2C_6H_5$, $R^8=CH_2CH_2COOCH_2C_6H_5$).

A mixture of N-benzyloxycarbonyl-S-octadecyl-D-cysteine (0.250 g, 0.49 mmol), L-glutamic acid dibenzyl ester (p-toluenesulfonate) (0.244 g, 0.49 mmol) and methylene chloride (15 ml) is added, at 0°C, with triethylamine (0.068 ml, 0.49 mmol) and dicyclohexylcarbodiimide (0.109 mg, 0.53 mmol). The mixture is stirred at room temperature for 3 h. Thereafter it is added with some drops of glacial acetic acid, stirred for 30 min and the formed dicyclohexylurea is filtered off. The filtrate is washed with water, dried and the volatiles are evaporated off, to obtain a crude product which is purified by flash chromatography on a silica gel column. Eluting with petroleum ether:chloroform,

1:1, 0.323 g of the title compound are recovered in form of a colourless oil (82% yield).

T.L.C.: ethyl ether, 2:1, R_f = 0.68

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.80 (t, 3H); 1.23 (m, 30H); 1.47 (m, 2H); 2.00 (m, 1H); 2.16 (m, 1H); 2.31 (m, 2H); 2.45 (m, 2H); 2.75 (m, 2H); 4.24 (m, 1H); 4.57 (m, 1H); 5.01 (s, 2H); 5.04 (s, 2H); 5.08 (d, 2H); 7.26 (m, 15H).

EXAMPLE 7

Benzyl N-benzyloxycarbonyl-S-octadecyl-D-cysteinyl-L-leucinate ((IV), X=S, $R^1=(CH_2)_{17}CH_3$, R^6 and $R^7=COOCH_2C_6H_5$, $R^8=CH_2CH(CH_3)_2$).

According to the procedure described in example 6 starting from N-benzyloxycarbonyl-S-octadecyl-D-cysteine and benzyl L-leucinate (hydrochloride), the title compound was prepared as a colourless oil (88% yield).

T.L.C.: eluent ethyl ether, R_f = 0.77

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.85 (t, 9H); 1.24 (m, 30H); 1.56 (m, 5H); 2.50 (m, 2H); 2.79 (dd, 1H); 2.92 (dd, 1H); 4.31 (m, 1H); 4.60 (m, 1H); 5.10 (m, 4H); 7.30 (m, 10H).

EXAMPLE 8

Benzyl N-benzyloxycarbonyl-S-octadecyl-D-cysteinylglycinate ((IV), X=S, $R^1=(CH_2)_{17}CH_3$, R^6 and $R^7=COOCH_2C_6H_5$, $R^8=H$).

According to the procedure described in example 6, starting from N-benzyloxycarbonyl-S-octadecyl-D-cysteine and benzyl glycinate (hydrochloride), the title compound was prepared as a colourless oil (76% yield).

T.L.C.: eluent ethyl ether, R_f = 0.66

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.90 (t, 3H); 1.21 (m, 30H); 1.56 (m, 2H); 2.50 (m, 2H); 2.82 (dd, 1H); 2.96 (dd, 1H); 4.06 (m, 2H); 4.36 (m, 1H); 5.11 (s, 2H); 5.16 (s, 2H); 7.32 (m, 10H).

EXAMPLE 9

Benzyl N-benzyloxycarbonyl-S-octadecyl-D-cysteinyl-ε-N-benzyloxycarbonyl-L-lysinate ((IV), X=S, $R_1=(CH_2)_{17}CH_3$, R^6 and $R^7=COOCH_2C_6H_5$, $R^8=(CH_2)_4NHCOOCH_2C_6H_5$).

According to the procedure described in example 6, starting from N-benzyloxycarbonyl-S-octadecyl-D-cysteine and benzyl ε-N-benzyloxycarbonyl-L-lysinate (hydrochloride), the title compound was prepared as a colourless oil (77% yield).

T.L.C.: eluent ethyl ether, R_f = 0.67

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.86 (t, 3H); 1.25 (m, 30H); 1.40-1.90 (complex signal, 8H); 2.48 (m, 2H); 2.84 (m, 2H); 3.05 (m, 2H); 4.30 (m, 1H); 4.58 (m, 1H); 5.10 (m, 6H); 7.30 (m, 15H).

EXAMPLE 10

Benzyl N-benzyloxycarbonyl-S-octadecyl-L-cysteinyl-ε-N-benzyloxycarbonyl-L-lysinate ((IV), X=S, $R^1=(CH_2)_{17}CH_3$, R^6 and $R^7=COOCH_2C_6H_5$, $R^8=(CH_2)_4NHCOOCH_2C_6H_5$).

According to the procedure described in example 6, starting from N-benzyloxycarbonyl-S-octadecyl-L-cysteine and benzyl ε-N-benzyloxycarbonyl-L-lysinate (hydrochloride), the title compound was prepared as a colourless oil (80% yield).

T.L.C.: eluent ethyl ether, R_f = 0.67

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.86 (t, 3H); 1.25 (m, 30H); 1.40-1.90 (complex signal, 8H); 2.48 (m, 2H); 2.84 (m, 2H); 3.05 (m, 2H); 4.30 (m, 1H); 4.58 (m, 1H);

5.10 (m, 6H); 7.30 (m, 15H).

EXAMPLE 11

Benzyl N-benzyloxycarbonyl-S-octadecyl-D-cysteinyl-ε-N-benzyloxycarbonyl-D-lysinate ((IV), X=S, $R^1=(CH_2)_{17}CH_3$, R^6 and $R^7=COOCH_2C_6H_5$, $R^8=(CH_2)_4NHCOOCH_2C_6H_5$).

According to the procedure described in example 6, starting from N-benzyloxycarbonyl-S-octadecyl-D-cysteine and benzyl ε-N-benzyloxycarbonyl-D-lysinate (hydrochloride), the title compound was prepared as a colourless oil (84% yield).

T.L.C.: eluent ethyl ether, R_f = 0.67

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.86 (t, 3H); 1.25 (m, 30H); 1.40-1.90 (complex signal, 8H); 2.48 (m, 2H); 2.84 (m, 2H); 3.05 (m, 2H); 4.30 (m, 1H); 4.58 (m, 1H); 5.10 (m, 6H); 7.30 (m, 15H).

EXAMPLE 12

Benzyl N-benzyloxycarbonyl-S-octadecyl-L-cysteinyl-ε-N-benzyloxycarbonyl-D-lysinate ((IV), X=S, $R^1=(CH_2)_{17}CH_3$, R^6 and $R^7=COOCH_2C_6H_5$, $R^8=(CH_2)_4NHCOOCH_2C_6H_5$).

According to the procedure described in example 6, starting from N-benzyloxycarbonyl-S-octadecyl-L-cysteine and benzyl ε-N-benzyloxycarbonyl-D-lysinate (hydrochloride), the title compound was prepared as a colourless oil (79% yield).

T.L.C.: eluent ethyl ether, R_f = 0.67

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.86 (t, 3H); 1.25 (m, 30H); 1.40-1.90 (complex signal, 8H); 2.48 (m, 2H); 2.84 (m, 2H); 3.05 (m, 2H); 4.30 (m, 1H); 4.58 (m, 1H); 5.10 (m, 6H); 7.30 (m, 15H).

EXAMPLE 13

Benzyl N-benzyloxycarbonyl-S-butyl-D-cysteinyl-γ-benzyl-L-glutamate ((IV), X=S, $R^1=(CH_2)_3CH_3$, R^6 and $R^7=COOCH_2C_6H_5$, $R^8=CH_2CH_2COOCH_2C_6H_5$).

According to the procedure described in example 6, starting from N-benzyloxycarbonyl-S-butyl-D-cysteine and L-glutamic acid dibenzyl ester (p-toluenesulfonate), the title compound was prepared as a colourless oil (92 % yield).

T.L.C.: eluent ethyl ether, R_f=0.57

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.88 (t, 3H); 1.35 (m, 2H); 1.50 (m, 2H); 2.02 (m, 1H); 2.24 (m, 1H); 2.40 (m, 2H); 2.50 (m, 2H); 2.88 (m, 2H); 4.39 (m, 1H); 4.69 (m, 1H); 5.10 (m, 6H); 7.26 (m, 15H).

EXAMPLE 14

Benzyl N-benzyloxycarbonyl-S-butyl-D-cysteinyl-L-leucinate ((IV), X=S, $R^1=(CH_2)_3CH_3$, R^6 and $R^7=COOCH_2C_6H_5$, $R^8=CH_2CH(CH_3)_2$).

According to the procedure described in example 6, starting from N-benzyloxycarbonyl-S-butyl-D-cysteine and benzyl L-leucinate (hydrochloride), the title compound was prepared as a colourless oil (96 % yield).

T.L.C.: eluent ethyl ether, R_f=0.57

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.87 (m, 9H); 1.34 (m, 2H); 1.58 (m, 5H); 2.50 (m, 2H); 2.86 (m, 2H); 4.37 (m, 1H); 4.64 (m, 1H); 5.08 (m, 4H); 7.28 (m, 10H).

EXAMPLE 15

Benzyl N-benzyloxycarbonyl-S-butyl-D-cysteinyl-ε-N-benzyloxycarbonyl-L-lysinate ((IV), X=S, $R^1=(CH_2)_3CH_3$, R^6 and $R^7=COOCH_2C_6H_5$, $R^8=(CH_2)_4NHCOOCH_2C_6H_5$).

According to the procedure described in example 6,

starting from N-benzyloxycarbonyl-S-butyl-D-cysteine and benzyl ε-N-benzyloxycarbonyl-L-lysinate (hydrochloride), the title compound was prepared as a colourless oil (85 % yield).

T.L.C.: eluent ethyl ether, R_f=0.38

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.85 (t, 3H); 1.20-1.90 (complex signal, 10H); 2.48 (t, 2H); 2.70 (dd, 1H); 2.88 (dd, 1H); 3.08 (m, 2H); 4.30 (m, 1H); 4.59 (m, 1H); 5.10 (m, 6H); 7.30 (m, 15H).

EXAMPLE 16

Benzyl S-octadecyl-D-cysteinyl-L-glutamate (hydrobromide) ((I), X=S, $R^1=(CH_2)_{17}CH_3$, R_2=H, $R^3=COOCH_2C_6H_5$, $R^4=CH_2CH_2COOH$).

A mixture of benzyl N-benzyloxycarbonyl-S-octadecyl-D-cysteinyl-γ-benzyl-L-glutamate (0.328 g, 0.40 mmol) and hydrobromic acid in 33% glacial acetic acid (4 ml) is stirred at room temperature for 30 min. After that, the mixture is evaporated to dryness to obtain the title compound as a colourless oil (100% yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.10

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.89 (t, 3H); 1.29 (m, 30H); 1.60 (m, 2H); 2.02 (m, 1H); 2.22 (m, 1H); 2.43 (m, 2H); 2.62 (m, 2H); 3.00 (m, 2H); 4.10 (m, 1H); 4.54 (m, 1H); 5.19 (m, 2H); 7.34 (m, 5H).

EXAMPLE 17

Benzyl S-octadecyl-D-cysteinyl-L-leucinate (hydrobromide) ((I), X=S, $R^1=(CH_2)_{17}CH_3$, R^2=H, $R^3=COOCH_2C_6H_5$, $R^4=CH_2CH(CH_3)_2$).

According to the procedure described in example 16, starting from benzyl N-benzyloxycarbonyl-S-octa-

decyl-D-cysteinyl-L-leucinate, the title compound was prepared as a colourless oil (95 % yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.47

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.85 (m, 6H); 1.20 (m, 30H); 1.56 (m, 5H); 2.58 (m, 2H); 3.15 (m, 2H); 3.74 (m, 1H); 4.50 (m, 1H); 5.28 (q, 2H); 7.30 (m, 5H).

EXAMPLE 18

S-Octadecyl-D-cysteinylglycine (hydrobromide) ((I), X=S, $R^1=(CH_2)_{17}CH_3$, R^2=H, R^3=COOH, R^4=H).

According to the procedure described in example 16, starting from benzyl N-benzyloxycarbonyl-S-octadecyl-D-cysteinylglycinate and after 4 h stirring at room temperature, the title compound was prepared (90 % yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.12

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.92 (t, 3H); 1.29 (m, 30H); 1.72 (m, 2H); 2.63 (t, 2H); 2.88 (dd, 1H); 3.12 (dd, 1H); 4.00 (s, 2H); 4.06 (m, 1H).

EXAMPLE 19

S-Octadecyl-D-cysteinyl-L-lysine (hydrobromide) ((I), X=S, $R^1=(CH_2)_{17}CH_3$, R^2=H, R^3=COOH, $R^4=(CH_2)_4NH_2$).

According to the procedure described in example 18, starting from benzyl N-benzyloxycarbonyl-S-octadecyl-D-cysteinyl-ε-N-benzyloxycarbonyl-L-lysinate, the title compound was prepared as a white solid which decomposes at 158°C (99 % yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.17

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.90 (t, 3H); 1.30

(m, 30H); 1.49-2.02 (complex signal, 8H); 2.65 (t, 2H); 2.89 (dd, 1H); 2.84 (t, 2H); 3.18 (dd, 1H); 4.16 (m, 1H); 4.44 (m, 1H).

EXAMPLE 20

S-Octadecyl-L-cysteinyl-L-lysine (hydrobromide) ((I), X=S, $R^1=(CH_2)_{17}CH_3$, R^2=H, R^3=COOH, $R^4=(CH_2)_4NH_2$).

According to the procedure described in example 18, starting from benzyl N-benzyloxycarbonyl-S-octadecyl-L-cysteinyl-ε-N-benzyloxycarbonyl-L-lysinate, the title compound was prepared (95 % yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.17

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.90 (t, 3H); 1.30 (m, 30H); 1.49-2.02 (complex signal, 8H); 2.65 (t, 2H); 2.89 (dd, 1H); 2.84 (t, 2H); 3.18 (dd, 1H); 4.16 (m, 1H); 4.44 (m, 1H).

EXAMPLE 21

S-Octadecyl-D-cysteinyl-D-lysine (hydrobromide) ((I), X=S, $R^1=(CH_2)_{17}CH_3$, R^2=H, R^3=COOH, $R^4=(CH_2)_4NH2$).

According to the procedure described in example 18, starting from benzyl N-benzyloxycarbonyl-S-octadecyl-D-cysteinyl-ε-N-benzyloxycarbonyl-D-lysinate, the title compound was prepared (88 % yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.17

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.84 (t, 3H); 1.30 (m, 30H); 1.49-2.02 (complex signal, 8H); 2.65 (t, 2H); 2.89 (dd, 1H); 2.84 (t, 2H); 3.18 (dd, 1H); 4.16 (m, 1H); 4.44 (m, 1H).

EXAMPLE 22

S-Octadecyl-L-cysteinyl-D-lysine (hydrobromide)

((I), X=S, $R^1=(CH_2)_{17}CH_3$, R^2=H, R^3=COOH, $R^4=(CH_2)_4NH2$).

According to the procedure described in example 18, starting from benzyl N-benzyloxycarbonyl-S-octadecyl-L-cysteinyl-ε-N-benzyloxycarbonyl-D-lysinate, the title compound was prepared as a colourless oil (97 % yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.17

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.90 (t, 3H); 1.30 (m, 30H); 1.49-2.02 (complex signal, 8H); 2.65 (t, 2H); 2.89 (dd, 1H); 2.84 (t, 2H); 3.18 (dd, 1H); 4.16 (m, 1H); 4.44 (m, 1H).

EXAMPLE 23

S-Butyl-D-cysteinyl-L-glutamic acid (hydrobromide)

((I), X=S, $R^1=(CH_2)_3CH_3$, R^2=H, R^3=COOH, $R^4=CH_2CH_2COOH$).

According to the procedure described in example 18, starting from benzyl N-benzyloxycarbonyl-S-butyl-D-cysteinyl-γ-benzyl-L-glutamate, the title compound was prepared (92 % yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.18

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.82 (t, 3H); 1.30 (m, 2H); 1.51 (m, 2H); 1.98 (m, 1H); 2.21 (m, 1H); 2.49 (t, 2H); 2.58 (t, 2H); 3.02 (m, 2H); 4.20 (t, 2H); 4.45 (m, 1H).

EXAMPLE 24

S-Butyl-D-cysteinyl-L-leucine (hydrobromide)

((I), X=S, $R^1=(CH_2)_3CH_3$, R^2=H, R^3=COOH, $R^4=CH_2CH(CH_3)_2$).

According to the procedure described in example 18, starting from benzyl N-benzyloxycarbonyl-S-butyl-D-

cysteinyl-L-leucinate, the title compound was prepared (98 % yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.38

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.80 (m, 9H); 1.28 (m, 2H); 1.68 (m, 3H); 2.54 (m, 2H); 3.03 (m, 2H); 4.31 (m, 2H).

EXAMPLE 25

S-Butyl-D-cysteinyl-L-lysine (hydrobromide) ((I), X=S, $R^1=(CH_2)_3CH_3$, R^2=H, R^3=COOH, $R^4=(CH_2)_4NH_2$).

According to the procedure described in example 18, starting from benzyl N-benzyloxycarbonyl-S-butyl-D-cysteinyl-ε-N-benzyloxycarbonyl-L-lysinate, the title compound was prepared (91 % yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.24

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.94 (t, 3H); 1.39-2.00 (complex signal, 10H); 2.67 (t, 2H); 2.96 (m, 3H); 3.14 (dd, 1H); 4.19 (t, 1H); 4.43 (m, 1H).

EXAMPLE 26

N-Acetyl-S-octadecyl-D-cysteinyl-L-glutamic acid ((I), X=S, $R^1=(CH_2)_{17}CH_3$, $R^2=COCH_3$, R^3=COOH, $R^4=CH_2CH_2COOH$).

A mixture of benzyl S-octadecyl-D-cysteinyl-L-glutamate (hydrobromide) (0.270 g, 0.40 mmol), acetic anhydride (0.038 ml, 0.40 mmol), triethylamine (0.067 ml, 0.48 mmol) and dry benzene (8 ml) is stirred at room temperature for 4 h. After that, the mixture is evaporated to dryness, diluted with chloroform (25 ml), washed with 0.2 M hydrochloric acid, dried and solvent is removed, to obtain a crude product, which is redis-

solved in a solution of hydrobromic acid in 33% acetic acid. The mixture is left under stirring at room temperature for 4 h. After that the mixture is evaporated to dryness, to obtain a crude product which is purified by flash chromatography on a functionalized silica gel column (SDS RP-18, 200-400 mesh). Eluting with water (0.045% trifluoroacetic acid):acetonitrile (0.035% trifluoroacetic acid), 2:3, 0.187 g of the title compound are recovered as a white solid melting at 118-120°C (86% yield).

$[\alpha]_D^{20}$ = +11.4° (c=0.440, methanol).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.15

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.92 (t, 3H); 1.29 (m, 30H); 1.58 (m, 2H); 1.97 (m, 1H); 2.00 (s, 3H); 2.19 (m, 1H); 2.43 (t, 2H); 2.56 (t, 2H); 2.73 (dd, 1H); 2.92 (dd, 1H); 4.44 (m, 1H); 4.55 (m, 1H).

EXAMPLE 27

N-Acetyl-S-octadecyl-D-cysteinyl-L-leucine ((I), X=S, $R^1=(CH_2)_{17}CH_3$, $R^2=COCH_3$, $R^3=COOH$, $R^4=CH_2CH(CH_3)_2$).

According to the procedure described in example 26, starting from benzyl S-octadecyl-D-cysteinyl-L-leucinate, the title compound was prepared as a white solid melting at 95-97°C (73 % yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.54

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.81 (t, 6H); 1.20 (m, 30H); 1.52 (m, 5H); 1.92 (s, 3H); 2.46 (t, 2H); 2.74 (m, 2H); 4.43 (m, 2H).

EXAMPLE 28

N-Acetyl-S-octadecyl-D-cysteinylglycine ((I), X=S, $R^1=(CH_2)_{17}CH_3$, $R^2=COCH_3$, $R^3=COOH$, $R^4=H$).

A mixture of S-octadecyl-D-cysteinylglycine (hydrobromide) (0.102 g, 0.24 mmol), acetic anhydride (0.030 ml, 0.31 mmol), triethylamine (0.084 ml, 0.60 mmol) and dry benzene (10 ml) is stirred at room temperature for 4 h. After that the mixture is evaporated to dryness, diluted with chloroform (25 ml), washed with 0.2 M hydrochloric acid, dried and solvent is removed, to obtain a crude product which is purified by flash chromatography on a functionalized silica gel column (SDS RP-18, 200-400 mesh). Eluting with water (0.045% trifluoroacetic acid):acetonitrile (0.035% trifluoroacetic acid), 1:1, 0.092 g of the title compound are recovered as a semisolid oil (81% yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, $R_f=0.42$

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.89 (t, 3H); 1.33 (m, 30H); 1.54 (m, 2H); 2.01 (s, 3H); 2.55 (t, 2H); 2.73 (dd, 1H); 3.00 (dd, 1H); 3.90 (s, 2H); 4.55 (m, 1H).

EXAMPLE 29

N-Acetyl-S-octadecyl-D-cysteinyl-ε-N-acetyl-L-lysine ((I), X=S, $R^1=(CH_2)_{17}CH_3$, $R^2=COCH_3$, $R^3=COOH$, $R^4=(CH_2)_4NHCOCH_3$).

According to the procedure described in example 28, starting from S-octadecyl-D-cysteinyl-L-lysine (hydrobromide), the title compound was prepared as a semisolid oil (67 % yield).

$[\alpha]_D^{20}$ = +4.5° (c=0.964, methanol).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.21

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.90 (t, 3H); 1.29 (m, 30H); 1.34-1.64 (complex signal, 6H); 1.73 (m, 1H); 1.89 (m, 1H); 1.92 (s, 3H); 2.02 (s, 3H); 2.56 (t, 2H); 2.74 (dd, 1H); 2.92 (dd, 1H); 3.14 (t, 2H); 4.39 (m, 1H); 4.58 (t, 1H).

EXAMPLE 30

N-Acetyl-S-octadecyl-L-cysteinyl-ε-N-acetyl-L-lysine ((I), X=S, $R^1=(CH_2)_{17}CH_3$, $R^2=COCH_3$, $R^3=COOH$, $R^4=(CH_2)_4NHCOCH_3$).

According to the procedure described in example 28, starting from S-octadecyl-L-cysteinyl-L-lysine (hydrobromide), the title compound was prepared as a solid melting at 120-122°C (72 % yield).

$[\alpha]_D^{20}$ = -5.9° (c=0.720, chloroform:methanol, 3:2).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.21

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.90 (t, 3H); 1.29 (m, 30H); 1.34-1.64 (complex signal, 6H); 1.73 (m, 1H); 1.89 (m, 1H); 1.92 (s, 3H); 1.84 (s, 3H); 2.56 (t, 2H); 2.71 (dd, 1H); 2.95 (dd, 1H); 3.15 (m, 2H); 4.38 (m, 1H); 4.52 (m, 1H).

EXAMPLE 31

N-Acetyl-S-octadecyl-D-cysteinyl-ε-N-acetyl-D-lysine ((I), X=S, $R^1=(CH_2)_{17}CH_3$, $R^2=COCH_3$, $R^3=COOH$, $R^4=(CH_2)_4NHCOCH_3$).

According to the procedure described in example 28, starting from S-octadecyl-D-cysteinyl-D-lysine (hydrobromide), the title compound was prepared as a white solid melting at 122-125°C (76 % yield).

$[\alpha]_D^{20}$ = +6.9° (c=0.865, chloroform:methanol, 3:2).
T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.21
N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.90 (t, 3H); 1.29 (m, 30H); 1.34-1.64 (complex signal, 6H); 1.73 (m, 1H); 1.89 (m, 1H); 1.92 (s, 3H); 2.00 (s, 3H); 2.56 (t, 2H); 2.71 (dd, 1H); 2.95 (dd, 1H); 3.15 (m, 2H); 4.38 (m, 1H); 4.52 (m, 1H).

EXAMPLE 32

N-Acetyl-S-octadecyl-L-cysteinyl-ε-N-acetyl-D-lysine ((I), X=S, $R^1=(CH_2)_{17}CH_3$, $R^2=COCH_3$, $R^3=COOH$, $R^4=(CH_2)_4NHCOCH_3$).

According to the procedure described in example 28, starting from S-octadecyl-L-cysteinyl-D-lysine (hydrobromide), the title compound was prepared as a white solid melting at 82-85°C (70 % yield).
$[\alpha]_D^{20}$ = -6.7° (c=0.72, methanol).
T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.21
N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.90 (t, 3H); 1.29 (m, 30H); 1.34-1.64 (complex signal, 6H); 1.73 (m, 1H); 1.89 (m, 1H); 1.92 (s, 3H); 2.02 (s, 3H); 2.56 (t, 2H); 2.74 (dd, 1H); 2.92 (dd, 1H); 3.14 (t, 2H); 4.39 (m, 1H); 4.58 (t, 1H).

EXAMPLE 33

N-Dodecanoyl-S-butyl-D-cysteinyl-L-glutamic acid ((I), X=S, $R^1=(CH_2)_3CH_3$, $R^2=CO(CH_2)_{10}CH3$, $R^3=COOH$, $R^4=CH_2CH_2COOH$).

A mixture of S-butyl-D-cysteinyl-L-glutamic acid (hydrobromide) (0.419 g, 1.08 mmol), dodecaneic anhydride (0.425 mg, 1.11 mmol), triethylamine (0.563 ml,

4.04 mmol) and dry chloroform (30 ml) is stirred at room temperature for 4 h. After that it is diluted with chloroform (50 ml), washed with 0.2 M hydrochloric acid, dried and solvent is removed, to obtain a crude product, which is purified by flash chromatography on a silica gel column. Eluting with chloroform:methanol, 4:1, 0.449 g of the title compound are recovered as a semisolid oil (85 % yield).

$[\alpha]_D^{20}$ = +22.7° (c=3.33, methanol).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.24

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.90 (m, 6H); 1.22-1.46 (complex signal, 18H); 1.56 (m, 4H); 1.96 (m, 1H); 2.18 (m, 1H); 2.25 (t, 2H); 2.40 (q, 2H); 2.55 (t, 2H); 2.73 (m, 1H); 2.93 (m, 1H); 4.44 (m, 1H); 4.56 (m, 1H).

EXAMPLE 34

N-Dodecanoyl-S-butyl-D-cysteinyl-L-leucine

((I), X=S, $R^1=(CH_2)_3CH_3$, $R^2=CO(CH_2)_{10}CH_3$, R^3=COOH, $R^4=CH_2CH(CH_3)_2$).

Following the process described in example 33, starting from S-octadecyl-L-cysteinyl-D-leucine (hydrobromide), the title compound was prepared as a semisolid oil (97 % yield).

$[\alpha]_D^{20}$ = +2.0° (c=5.40, methanol).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.69

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.92 (m, 12H); 1.22-1.84 (complex signal, 25H); 2.34 (t, 2H); 2.59 (t, 2H); 2.78 (dd, 1H); 2.89 (dd, 1H); 4.38 (m, 1H); 4.53 (m, 1H).

EXAMPLE 35

N-Acetyl-S-butyl-D-cysteinyl-ε-N-acetyl-L-lysine ((I), X=S, $R^1=(CH_2)_3CH_3$, $R^2=COCH_3$, $R^3=COOH$, $R^4=(CH_2)_4NHCOCH_3$).

According to the procedure described in example 28, starting from S-butyl-D-cysteinyl-L-lysine (hydrobromide), the title compound was prepared as a semisolid oil (88 % yield).

$[\alpha]_D^{20}$ = +30.5° (c=1.23, methanol).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.29

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.92 (t, 3H); 1.39-1.64 (complex signal, 8H); 1.74 (m, 1H); 1.86 (m, 1H); 1.91 (s, 3H); 1.99 (s, 3H); 2.56 (t, 2H); 2.72 (dd, 1H); 2.92 (dd, 1H); 3.14 (t, 2H); 4.38 (m, 1H); 4.56 (t, 1H).

EXAMPLE 36

S-Octadecyl-D,L-cysteine (hydrobromide) ((II), X=S, $R^1=(CH_2)_{17}CH_3$, R^6=H).

Following the process described in example 18, starting from N-benzyloxycarbonyl-S-octadecyl-D,L-cysteine, the title compound was prepared as a white solid which decomposes at 230°C (95% yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.05

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.92 (t, 3H); 1.34 (m, 30H); 1.65 (m, 2H); 2.65 (t, 2H); 3.04 (dd, 1H); 3.18 (dd, 1H); 4.22 (dd, 1H).

EXAMPLE 37

N-Acetyl-S-octadecyl-D,L-cysteine ((II), X=S, $R^1=(CH_2)_{17}CH_3$, $R^6=COCH_3$).

Following the process described in example 28, starting from S-Octadecyl-D,L-cysteine (hydrobromide), the title compound was prepared as a white solid melting at 96-99°C (87% yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.53

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.85 (t, 3H); 1.25 (m, 30H); 1.55 (m, 2H); 2.06 (s, 3H); 2.50 (t, 2H); 2.99 (m, 2H); 4.72 (m, 1H).

EXAMPLE 38

N-Acetyl-S-octadecyl-D,L-cysteinyltaurine (sodium salt).

((I), X=S, $R^1=(CH_2)_{17}CH_3$, $R^2=COCH_3$, $R^3=H$, $R^4=CH_2SO_3Na$).

A solution of N-acetyl-S-octadecyl-D,L-cysteine (0.231 g, 0.55 mmol) and N-hydroxy-5-norbornen-2,3-dicarboxymide acid (0.109 g, 0.61 mmol) in tetrahydrofuran:dioxane, 1:1 (6 ml), is added at 0°C with dicyclohexylcarbodiimide (0.127 g, 0.61 mmol). The mixture is stirred for 2 h a 0°C and for 20 h at room temperature. After that, the formed dicyclohexylurea is filtered off and the filtrate is evaporated to dryness. The resulting residue is redissolved in dioxane (2.5 ml) and added with a solution of taurine (0.078 g, 0.62 mmol) in a 0.42 M sodium bicarbonate solution (1.5 ml). The mixture is stirred for 20 h at room temperature, evaporated to dryness and the resulting crude product is digested with ethyl acetate. The insoluble residue is dissolved in chloroform (300 ml), washed with 2 M hydrochloric acid and dried and solvent is removed, to obtain a crude product which is purified by flash chromatography on a functionalized silica gel column (SDS

RP-18, 200-400 mesh). Eluting with water (0.045% trifluoroacetic acid):acetonitrile (0.035% trifluoroacetic acid), 3:2, 0.234 g of the title compound are recovered as a white solid which decomposes at 168°C (78% yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.24

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.89 (t, 3H); 1.29 (m, 30H); 1.58 (m, 2H); 1.92 (s, 3H); 2.55 (t, 2H); 2.71 (m, 1H); 2.96 (m, 3H); 3.59 (m, 2H); 4.44 (m, 1H).

EXAMPLE 39

1-O-Octadecyl-2-acetylamino-3-deoxyglycerol. ((XI), $R^1=(CH_2)_{17}CH_3$, $R^6=COCH_3$).

Following the process described in example 28, starting from 1-O-octadecyl-2-amino-3-deoxyglycerol the title compound was prepared as a white solid melting at 71-72°C (90% yield).

T.L.C.: eluent chloroform:methanol, 9:1, R_f=0.43

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.85 (t, 3H); 1.24 (m, 30H); 1.55 (m, 2H); 2.00 (s, 3H); 3.40 (t, 2H); 3.50-3.68 (complex signal, 3H); 3.80 (dd, 1H); 4.03 (m, 1H).

EXAMPLE 40

N-Acetyl-O-octadecyl-D,L-serine. ((II), X=O, $R^1=(CH_2)_{17}CH_3$, $R^6=COCH_3$).

A solution of 1-O-octadecyl-2-acetylamino-3-deoxyglycerol (0.398 g, 1.03 mmol) in carbon tetrachloride:acetonitrile:water, 1:1:1.4 (37 ml) is added with $NaIO_4$ (0.909 g, 4.24 mmol) and $RuCl_3.3H_2O$ (8.2 mg, 0.031 mmol). The mixture is stirred for 1.5 h at room temperature. After that, water (7 ml) and methylene chloride (7 ml) are added, the two formed phases are

separated and the aqueous one is extracted with methylene chloride. The combined organic phases are dried and solvent is removed, to obtain a crude product which is purified by flash chromatography on silica gel column. Eluting with chloroform:methanol, 97.5:2.5, 0.346 g of the title compound are recovered as a white solid melting at 86-89°C (82% yield).

T.L.C.: eluent chloroform:methanol:water, 64:25:4, R_f=0.35

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.85 (t, 3H); 1.25 (m, 30H); 1.52 (m, 2H); 2.02 (s, 3H); 3.42 (t, 2H); 3.62 (dd, 1H); 3.86 (dd, 1H); 4.68 (m, 1H).

EXAMPLE 41

N-Acetyl-O-octadecyl-D,L-serinyl-γ-benzyl-L-glutamate. ((IV), X=O, $R^1=(CH_2)_{17}CH_3$, $R^6=COCH_3$, $R^7=COOCH_2C_6H_5$, $R^8=CH_2CH_2COOCH_2C_6H_5$).

According to the procedure described in example 6, starting from N-acetyl-O-octadecyl-D,L-serine and L-glutamic acid dibenzyl ester (p-toluenesulfonate), the title compound was prepared as a colourless oil (83% yield).

T.L.C.: eluent chloroform:methanol, 9:1, R_f = 0.54

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.85 (t, 3H); 1.25 (m, 30H); 1.50 (m, 2H); 1.99(m, 1H); 2.00 (s, 3H); 2.21 (m, 1H); 2.38 (m,2H); 3.39 (m, 3H); 3.76 (dd, 1H); 4.51 (m, 1H); 4.63 (m, 1H); 5.08 (s, 2H); 5.12 (s, 2H); 7.32 (m, 10H).

EXAMPLE 42

N-Acetyl-O-octadecyl-D,L-serinyl-L-leucinate ((IV), X=O, $R^1=(CH_2)_{17}CH_3$, $R^6=COCH_3$, $R^7=COOCH_2C_6H_5$, $R^8=CH_2CH(CH_3)_2$).

According to the procedure described in example 6, starting from N-acetyl-O-octadecyl-D,L-serine and benzyl L-leucinate (hydrochloride), the title compound was prepared as a colourless oil (92 % yield).

T.L.C.: eluent chloroform:methanol:water, 64:25:4, R_f=0.50

N.M.R. ^1H (300 MHz, $CDCl_3$) δ ppm: 0.87 (m, 9H); 1.21 (m, 30H); 1.61 (m, 5H); 1.98 (s, 3H); 3.42 (m, 3H); 3.78 (m, 1H); 4.50 (m, 1H); 4.62 (m, 1H); 5.12 (s, 2H); 7.32 (m, 5H).

EXAMPLE 43

N-Acetyl-O-octadecyl-D,L-serinyl-L-glutamic acid ((I), X=O, $R^1=(CH_2)_{17}CH_3$, $R^2=COCH_3$, $R^3=COOH$, $R^4=CH_2CH_2COOH$).

A solution of benzyl N-acetyl-O-octadecyl-D,L-serinyl-γ-benzyl-L-glutamate (0.100 g, 0.14 mmol) in glacial acetic acid (10 ml) is added with 0.015 g of 10% palladium-on-carbon and the mixture is stirred for 18 h at room temperature, under hydrogen atmosphere, then it is filtered and evaporated to dryness, to obtain a crude product which is purified by flash chromatography on a functionalized silica gel column (SDS RP-18, 200-400 mesh). Eluting with water (0.045% trifluoroacetic acid):acetonitrile (0.035% trifluoroacetic acid), 2:3, 0.056 g of the title compound are recovered as a semi-solid oil (73 % yield).

T.L.C.: eluent chloroform:methanol:water, 65:25:4, R_f=0.14

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.90 (t, 3H); 1.28 (m, 30H); 1.56 (m, 2H); 1.95 (m, 1H); 2.02 (s, 3H); 2.20 (m, 1H); 2.41 (m,2H); 3.46 (m, 2H); 3.65 (m, 2H);

4.46 (m, 1H); 4.58 (m, 1H).

EXAMPLE 44

N-Acetyl-O-octadecyl-D,L-serinyl-L-leucine ((I),X=O, $R^1=(CH_2)_{17}CH_3$, $R^2=COCH_3$, $R^3=COOH$, $R^4=CH_2CH(CH_3)_2$).

According to the procedure described in example 43, starting from benzyl N-acetyl-O-octadecyl-D,L-serinyl-L-leucinate, the title compound was prepared as a semisolid oil (93 % yield).

T.L.C.: eluent chloroform:methanol:water, 64:25:4, R_f=0.65

N.M.R. ^1H (300 MHz, CD_3OD) δ ppm: 0.92 (m, 9H); 1.29 (m, 30H); 1.49-1.74 (complex signal, 5H); 2.00 (s, 3H); 3.46 (m, 2H); 3.65 (m, 2H); 4.45 (m, 1H); 4.58 (m, 1H).

EXAMPLE 45

Determination of the inhibition on phospholipase A_2.

The PLA_2 activity is determined by radioactive evaluation of the labelled fatty acid which esterifies the sn-2 position of the phospholipid substrate and which is released by the enzyme action. E. coli phospholipid membranes, to which labelled oleic acid (1-^{14}C) has previously been incorporated, are used as the substrate. The used enzyme is purified PLA_2 from human synovial liquid.

The reaction mixture contains 25 mM Hepes buffer (pH 7.0), 5.0 mM Ca^{2+} and 1.4x106 E. coli autoclaved (corresponding to 10000 dpm and 10.0 nmol of phospholipid). The reaction is started by addition of 80 ng of purified enzyme, keeping stirring for 5 minutes at 37°C. The reaction is stopped by adding 3.0 ml of $CHCl_3$:CH_3OH (1:2 v/v), the lipids are extracted by the

Bligh and Dyer procedure and the reaction products are separated by thin layer chromatography and dpm are quantified by liquid scintillation.

The study of the inhibiting effect on PLA_2 on the compounds of the present invention is carried out dissolving them in dimethylsulfoxide or ethanol and adding them to the above described reaction mixture until the required proportion. The hydrolysis percentage is calculated by means of the following equation:

$$\% \text{ Hydrolysis} = \frac{\text{free fatty acid (dpm)}}{\text{non hydrolyzed phospholipid+free fatty acid (dpm)}}$$

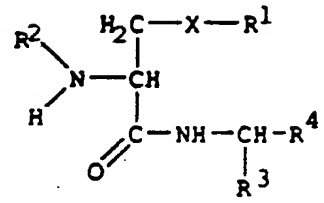
The compounds of the present invention were tested according to this procedure. The inhibiting action of the different compounds is expressed as the product concentration inhibiting the activity of the enzyme by 50% compared with the control in the absence of inhibitor (IC_{50}). Some examples of the obtained results are reported in the following Table.

Inhibiting effect on PLA_2 from human synovial liquid

Compound of Example Nº	IC_{50} (μM)
26	20
27	30
29	15
28	15
34	25
38	15
43	20
44	20

CLAIMS

1. Compounds of general formula (I)



I

wherein:

- X is an oxygen or sulphur atom;
- R^1 is a C_4-C_{20} straight or branched alkyl group;
- R^2 is hydrogen or a R^5-CO-, R^5-O-CO- or R^5-SO_2- group, in which R^5 is a C_1-C_{20} straight or branched alkyl group, phenyl or an arylalkyl group of less than 20 carbon atoms totally;
- R^3 is hydrogen, a carboxy group, an alkoxycarbonyl, aryloxycarbonyl or arylalkoxycarbonyl group of less than 10 carbon atoms in the last three cases;
- R^4 is hydrogen, a C_1-C_6 straight or branched alkyl group, an arylalkyl group of less than 10 carbon atoms, an heteroarylalkyl group of less than 10 carbon atoms, an hydroxyalkyl group of less than 4 carbon atoms, a thioalkyl or alkylthioalkyl group of less than 4 carbon atoms, an aminoalkyl group of less than 6 carbon atoms, the amino group being in the free or derivatized form, as an alkyl amide of less than 4 carbon atoms, a C_2-C_5 carboxyalkyl group, the carboxy group being in the free or derivatized form as an alkyl or aralkyl ester of less than 8 carbon atoms, a carbamoylalkyl group of less than 4 carbon atoms, a guanidinoalkyl group of

less than 5 carbon atoms, or a sulfoalkyl group of less than 4 carbon atoms; with the proviso that R^4 cannot be hydrogen when R^3 is hydrogen or when R^1 is C_4 alkyl and R^2 is hydrogen or acetyl;

and the pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1 characterized in that R^3 is hydrogen or a carboxy group, R^4 is a sulfomethyl group, or the group

$$-NH-\underset{R^3}{\underset{|}{CH}}-R^4$$

in formula (I) is an amino acid selected from glycine, lysine with the ε-amino in the free or alkylcarbonylamino form of less than 4 carbon atoms, leucine or glutamic acid with the γ-carboxyl in the free or alkoxycarbonyl or arylalkoxycarbonyl form of less than 8 carbon atoms.

3. Compounds according to claim 2 characterized in that R^2 is hydrogen or a R^5CO- group, wherein R^5 is a C_1-C_{20} straight alkyl group.

4. Compounds according to claim 3 characterized in that the group

$$-NH-\underset{R^3}{\underset{|}{CH}}-R^4$$

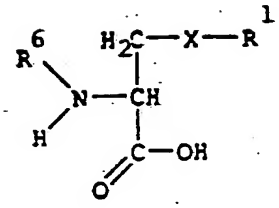
in formula (I) is an amino acid selected from glycine, lysine with the ε-amino in the free or alkylcarbonylamino form of less than 4 carbon atoms, leucine or glutamic acid with the γ-carboxyl in the free or alkoxycarbonyl or arylalkoxycarbonyl form of less than 8 carbon atoms.

5. Compounds according to claim 3 characterized in

that R^3 is hydrogen and R^4 is a sulfomethyl group.

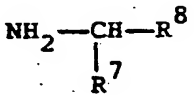
6. As compounds according to claim 1:
N-acetyl-O-octadecyl-D,L-serinyl-L-glutamic acid;
N-acetyl-O-octadecyl-D,L-serinyl-L-leucine;
S-octadecyl-D-cysteinylglycine (hydrobromide);
S-octadecyl-D-cysteinyl-L-lysine (hydrobromide);
S-octadecyl-L-cysteinyl-L-lysine (hydrobromide);
S-octadecyl-D-cysteinyl-D-lysine (hydrobromide);
S-octadecyl-L-cysteinyl-D-lysine (hydrobromide);
S-butyl-D-cysteinyl-L-glutamic acid (hydrobromide);
S-butyl-D-cysteinyl-L-leucine (hydrobromide);
S-butyl-D-cysteinyl-L-lysine (hydrobromide);
N-acetyl-S-octadecyl-D-cysteinyl-L-leucine;
N-acetyl-S-octadecyl-D-cysteinylglycine;
N-acetyl-S-octadecyl-D-cysteinyl-ε-N-acetyl-L-lysine;
N-acetyl-S-octadecyl-L-cysteinyl-ε-N-acetyl-L-lysine;
N-acetyl-S-octadecyl-D-cysteinyl-ε-N-acetyl-D-lysine;
N-acetyl-S-octadecyl-L-cysteinyl-ε-N-acetyl-D-lysine;
N-dodecanoyl-S-butyl-D-cysteinyl-L-glutamic acid;
N-dodecanoyl-S-butyl-D-cysteinyl-L-leucine;
N-acetyl-S-butyl-D-cysteinyl-ε-N-acetyl-L-lysine;
N-acetyl-S-octadecyl-D,L-cysteinyltaurine (sodium salt).

7. A process for the preparation of compounds of general formula (I) wherein R_4 is different from a sulfoalkyl group, comprising the reaction of a compound of formula (II) of suitable stereochemistry at the 2-carbon



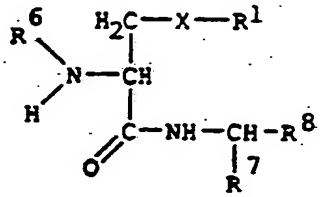
II

wherein X and R^1 have the same meanings as in claim 1 and R_6 has the same meanings as R_2 or, if R_2 is hydrogen, R_6 is a suitable amino-protecting group; with a compound of formula (III):



III

wherein R_7 and R_8 are the same as R_3 and R_4 as defined in claim 1, respectively, or they are groups which can be converted into R_3 and R_4, to give a compound of formula (IV):



IV

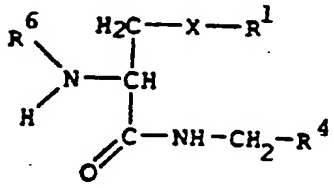
which is converted into compounds (I) by removing the optional protective groups in R_6, R_7 and R_8 groups.

8. A process for the preparation of compounds of general formula (I) wherein R_4 is a sulfoalkyl group and R_3 is hydrogen, comprising the reaction of a compound (II) as defined in claim 7 with a carboxy-activating agent in the presence of a dehydrating agent, followed

by reaction with a compound (V)

$$NH_2-CH_2-R^4 \qquad V$$

wherein R_4 is a sulfoalkyl group of less than 4 carbon atoms, to give a compound of formula (VI)



VI

wherein X, R^1, R^4 and R^6 are as defined in the previous claims, which compound (VI) is then converted to compounds (I) by removing the optionally present protecting groups.

9. The use of the compounds of claims 1 to 6 for the preparation of a medicament for the therapeutical treatment of inflammatory and allergic diseases, rheumatoid arthritis, tendinitis, bursitis, psoriasis, bronchial asthma and the like.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/00866

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07K5/06; C07C323/60; A61K37/02; A61K31/16

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07K ; C07C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	DE,A,2 728 462 (TAKEDA CHEMICAL INDUSTRIES) 5 January 1978 see reference example 4 on page 13 ff. ---	1,2,7
X	GB,A,1 417 318 (AKZO) 10 December 1975 see examples 1.A.1.-1.A.2. ---	1,7
X	DE,A,1 964 798 (CIBA) 16 July 1970 see example 3 ---	1,7

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 AUGUST 1993	02 -09- 1993
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FUHR C.K.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	ORGANIC SYNTHESES vol. 59, 1979, pages 159 - 169 A.M. FELIX ET AL. 'Removal of N-alpha-Benzyloxycarbonyl Groups from Sulfur-containing Peptides by Catalytic Hydrogenation in Liquid Ammonia: O-tert-Butyl-L-Seryl-S-tert-Butyl-L-Cysteine tert-Butyl Ester' see formulas on page 159 see page 161, paragraph 2 - page 162, paragraph 1 see note 11 on pages 163-165 ---	1,7
X	CHEMICAL AND PHARMACEUTICAL BULLETIN vol. 26, no. 5, May 1978, TOKYO JP pages 1576 - 1585 O. NISHIMURA ET AL. 'New Method for Removing the S-p-Methoxybenzyl and S-t-Butyl Groups from Cysteine Residues with Mercuric Trifluoroacetate' see page 1581, paragraph 5 see page 1581, paragraph 8 ---	1,2,7
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X	JOURNAL OF ORGANIC CHEMISTRY vol. 46, no. 9, April 1981, EASTON US pages 1868 - 1873 J.J. PASTUSZAK AND A. CHIMIAK 'tert-Butyl Group as Thiol Protection in Peptides Synthesis' see page 1869, right column, paragraph 4 see page 1872, left column, paragraph 3 -paragraph 4 ---	1,7
X	BIOPOLYMERS vol. 22, no. 12, December 1983, pages 2523 - 2538 P. PALLAI ET AL. 'Extended Retro-Inverso Analogs of Somatostatin' see page 2530, paragraph 3 - page 2531, paragraph 1 see page 2534, paragraph 3 - page 2535, paragraph 1 --- -/--	1-4,7

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	PEPTIDES vol. 11, no. 5, 1990, pages 983 - 988 G.A. GACEL ET AL. 'Synthesis, Biochemical and Pharmacological Properties of BUBUC, a highly Selective and Systemically Active Agonist for In Vivo Studies of delta-Opioid Receptors' see page 984, right column, paragraph 2 -paragraph 3	1-4,7
X	INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH vol. 38, no. 6, December 1991, COPENHAGEN DK pages 562 - 568 K. BARLOS ET AL. 'Solid phase synthesis of partially protected and free peptides containing disulphide bonds by simulaneous cysteine oxidation-release from 2-chlorotrityl resin' see page 567, left column, line 8	1

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9300866
SA 72814

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The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 18/08/93

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